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Editor

*New Research on*  
**Biofeedback**

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*Chapter II*

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## **Cortical Network of Auditory Feedback on Hand Action: A Functional MRI Study**

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### **Abstract**

Many neurophysiologic studies of the human brain concerning attention to sensory events without motor planning have been carried out to delineate multimodal sensorimotor networks. However, little is known about activation via different sensory modalities in humans in the process of monitoring ongoing movements with respect to improvement of planning and execution (sensorimotor transformation). We sought to evaluate effects of auditory feedback on voluntary hand movement in healthy volunteers and patients with deep sensory disturbance, and assure its cortical network.

Experiment I: By attaching a sound source to the second fingertip of the affected hand, four patients with deep sensory disturbance showed great improvement without visual information in voluntary movements of the affected hand owing to utilization of the sound information. This improvement was also observed in monaural patients. Utilization of auditory information in voluntary movements in humans is confirmed.

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Experiment II: Eight healthy subjects with a position sensor on the left second fingertip learned sound pitch changes in relation to the positions of the sensor by repetitively moving his left hand left-to-right or vice versa horizontally for 10 min. When the subject then closed eyes and moved the left hand longitudinally listening to the same sound with changing pitches, the hand movements shifted laterally in a manner similar to the adaptation. This finding proves that voluntary movement control is subconsciously affected by auditory information in healthy humans.

Experiment III: Six right-handed male subjects (age range, 21 to 26 years) with no neurologic or psychiatric history participated in this functional magnetic resonance imaging study. Five paradigms were carried out: SMP(repetitive pinching movement of the right hand with eyes closed), VS (watching visual signals), AS(listening to auditory signals), VMP(repetitive pinching movements of the right hand with real-time visual feedback), and AMP (repetitive pinching movements of the right hand with real-time auditory feedback). Conjunction analyses of VMP and AMP disclosed activation of the left superior temporal sulcus (STS) and left ventral premotor cortex (PMv)( $p < 0.05$ , FWE, corrected). Interaction analysis between VMP, SMP, and VS [VMP – (SMP+VS)] showed that both right and left intraparietal sulci (IPS) were involved in transforming the visual information. Interestingly, interaction between AMP, SMP, and AS [AMP – (SMP+AS)] showed engagement of the lateral region of the primary auditory cortex (A1) on the left side in transforming auditory information. This is the first report to implicate the left lateral A1 in transforming auditory information in controlling hand movements. In the sensorimotor transformation, both visual and auditory information concerning hand movements was transformed to the same STS and PMv area via modality-specific cortical networks.

Animals freely use a variety of sensory information for motor control. The development of sensory organs varies depending upon animal species, and for example, bats can guide their flights by emitting ultrasonic vocal signals and listening to echoes returning to their ears from objects in ambient spaces [1, 2]. Regarding the control of voluntary movements of four extremities in humans, the visual and somatic senses, and the sense of equilibrium are said to be utilized as main sources of information. In the present study, we investigated the effect of auditory feedback on the control of voluntary movements of limbs in humans.

## **1. Experiment I: Patients with Deep Sensory Disturbance Can Use Auditory Feedback to Control Voluntary Hand Action**

We further investigated on whether patients with deep sensory disturbance could utilize auditory information for controlling voluntary movements. It is known that the human has flexible latent abilities and a latent ability often develops to compensate a born disability. For example, blind persons are known to develop an ability to perceive spatial surroundings through auditory information[3, 4], and a sense to feel a change in ambient fields due to the presence of obstacles as a facial pressure is called as the facial vision [5]. A kind of motor control disturbances due to the deficit of somatosensory information, is known to be improved by supplemental use of visual feedback. Auditory feedback, however, has not been ascertained yet to be able to improve somatosensory disturbances. Can auditory feedback improve voluntary movements in patients with somatosensory disturbance? To answer this

question, we investigated, as the second experiment, the effect of auditory feedback on motor control in patients with deep sensory disturbance.

## 1.1. Subjects and Methods

### 1.1.1. Subjects

Four patients with deep sensory disturbance were evaluated with regard to the improvement of ataxia by utilization of auditory information (Table 1).

**Table 1 Characteristics of subjects with deep sensory disturbance**

No	Age / gender	Diagnosis	Affected side	Average hearing level (dB)	
				Right	Left
1	56y.o. / male	Thalamic hemorrhage	right	28.3	scale over
2	65y.o. / male	Thalamic hemorrhage	left	36.7	35.8
3	49y.o. / female	Thalamic hemorrhage	left	18.6	12.4
4	41y.o. / female	Guillain Barre syndrome	bilateral	10.8	6.7

### 1.1.2. Task Procedure

We investigated, as the first experiment, the effect of auditory feedback on motor control in patients with deep sensory disturbance by attaching a sound source and a position sensor on the second fingertip of patient's affected arm. We used natural sounds (broad noises from a small loudspeaker) and evaluated the effect of auditory information.

The finger-nose test (FNT) which is the test used in neurology to evaluate patient's dexterity in the movement of touching the nose with the tip of the second finger was employed, and the results were evaluated by means of three-dimensional analysis. Sound information was given from a small loudspeaker attached to the tip of the second finger of patient's affected left arm. FNT was carried out under the following two conditions: FNT without sound (Condition S-) and FNT with a sound from the loudspeaker (Condition S+). The subject closed eyes and performed Conditions S- and S+ alternately 4 times for each at intervals of 5 minutes.

### 1.1.3. Experimental Setup

All experiments were conducted in a sound-attenuated recording room. Each subject sat down on an exclusive chair with his head fixed. A small loudspeaker and the magnetic position sensor (Fastrak, Polhemus Incorporated, USA) were attached to the tip of the 2nd finger of his affected left hand, and the left hand was put on the table placed in front of him. The subject was instructed to take the starting posture with a shoulder flexion of 45 degrees, elbow flexion of 45 degrees, elbow supination of 90 degrees and wrist flexion of 0 degree. Three-dimensional tracing using the Fastrak sensor of the locus of hand movements was started when the hand left the table and completed when the finger touched subject's nose. The Fastrak sensor could detect 0.08 cm RMS in position and 0.15 degree RMS in angle, with a sampling rate of 60 Hz. The subject was instructed to intentionally use the sound

information (broad noises from the loudspeaker) during the performance of FNT. The broad noises were tuned to be 55 dB at subjects' ears when it was generated at the start point, and were generated for a period from 5 seconds before starting FNT to the completion of FNT.

## 1.2. Results

The results of the experiments reproduced the same trend in relation with the presence or absence of auditory feedback (Figure 1). As shown in Figure 2-a and -b, the mean length of a finger movement reaching the nose was significantly shorter in Condition S+ than in Condition S-, demonstrating that persons with disturbed somatic and visual senses utilized auditory feedback for controlling their voluntary movements ( $p < 0.01$ , Welch's modified two sample t-test).

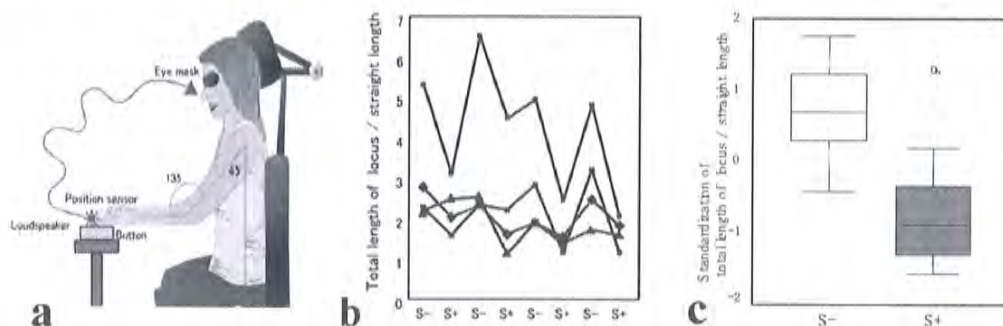


Figure 1. (a) Experimental set-up of the finger nose test (FNT). Each of four subjects closed eyes and repeatedly performed FNTs in both Conditions at intervals of 5 minutes. (b) Effect of sound information on the FNT in patients with deep sensory disturbance. The X axis shows Conditions, and the Y axis is the score of the total length of locus divided by the straight length of FNT. Conditions S+ and S- were FNTs with and without the sound from the loudspeaker, respectively. The results reproduced the same trend; scores in Condition S+ were smaller than those in Condition S-, indicating longer distances of the locus without sound information. (c) The mean value of standardized scores of the total length of locus divided by the straight length of FNT. The X-axis shows Conditions of each subject, and the Y-axis is the standardized score of the total length of locus divided by the straight length of FNT. Standardized scores in condition S+ were statistically significantly different from those in Condition S-. ( $p < 0.01$ , Welch's modified two sample t-test)

The variance of finger movement velocities in repeated FNTs was calculated in the lateral, longitudinal and vertical directions separately. When the finger reached the nose more rapidly, the variance became smaller, indicating more smooth movement. As shown in Figure 3, the subjects (No. 2-4) with binaural listening showed decreases in variance in the lateral direction, and the total length of loci was consequently decreased by this lateral improvement in these subjects.

It was notable that the subject (No. 1), who had no left hearing, could still use auditory information. In this subject, utilization of sound information decreased the variance markedly in the longitudinal direction, resulting in a decrease in the total length of loci. This case suggests that the mechanism of the effect of auditory feedback on the control of involuntary

movements cannot be explained not only from the result of sound localization by binaural listening but also from other auditory cues such as the sound intensity.

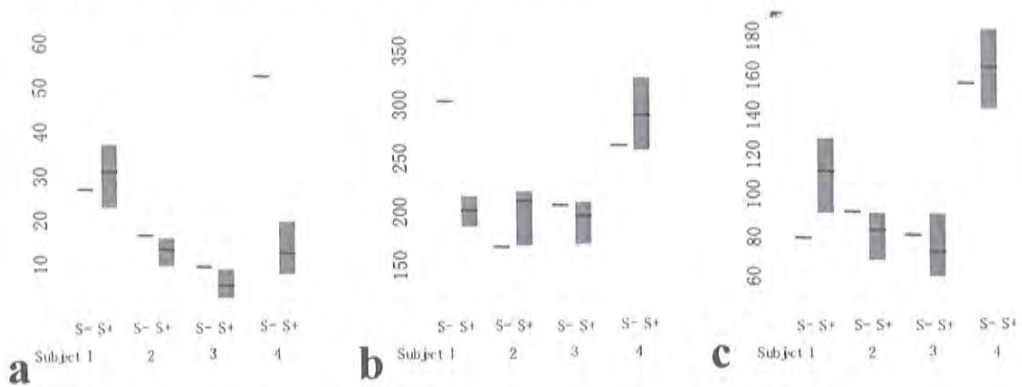


Figure 2. The variance of movement velocities in FNT. (a) The variance in the lateral direction. Subjects No. 2-4 with binaural listening demonstrated decreases in the variance. However, Subject No. 1 with monaural listening did not show improvement. (b) The variance in the longitudinal direction, and (c) the variance in the vertical direction. Subject No. 1 with monaural listening showed a marked decrease in the variance in the longitudinal direction. The variance may be an index of the degree of smooth movement, since the decrease of variance means that the hand moved more equally. The improvement of movement disturbance in one direction may lead to a decrease in the total length of loci.

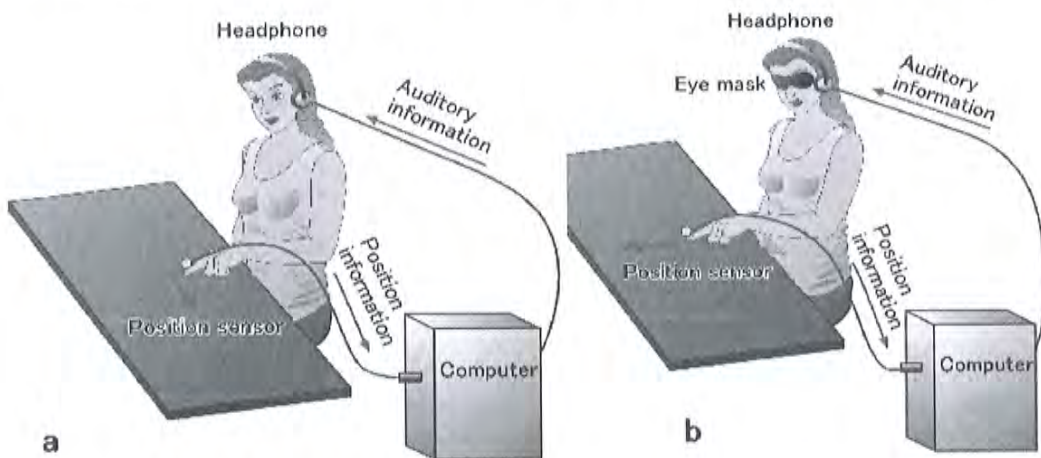


Figure 3. Experimental setup in the experiment II. (a) The subject sat down on an exclusive chair with his head fixed on a headrest. A magnetic position sensor was attached to the tip of the left 2nd finger, and the left hand was put on the table placed in front of him. Two-dimensional tracing of loci was performed when the subject repeatedly moved his left hand in the lateral direction as adaptation. The computer immediately modulated position signals to the sound whose pitch changed as the left arm was moved horizontally from left to right and vice versa. (b) After this learning phase, the subject was blinded with an eye mask and performed the reaching movement in the longitudinal direction listening to the same sound with changing pitches as the arm moved forward.

## 2. Experiment II: Healthy Volunteers Subconsciously are Affected by Auditory Feedback on Voluntary Hand Action

When visual, somatosensory and auditory signals are given simultaneously to a healthy human subject as learning information for voluntary movements, motor control learning is sufficiently established only by visual and somatic senses, and, as a consequence, the delicate influence of audition cannot be evaluated separately. Thus, we designed new experimental conditions based on the conditioning reported previously [6], that is, when the spatially moving sound synchronized with serially changing pitches is given to a subject for about 10 minutes, the subject becomes to feel as if a sound source is spatially moving despite that the subject is actually listening only to a sound with changing pitches but without any spatial moving. This effect is called a contingent auditory aftereffect.

### 2.1 Subjects and Methods

#### 2.1.1. Subjects

Eight right-handed healthy volunteers (5 males, mean age  $\pm$  s.d.,  $22.5 \pm 2.6$  years) participated in the study.

#### 2.1.2. Task Procedure

A position sensor was attached to the tip of the left second finger of each healthy volunteer subject, and the subject was adapted for 10 minutes to the sound whose pitch changed as the left arm was moved horizontally from left to right and vice versa (Figure 4a, 5a). After this learning phase, the subject closed eyes and performed the reaching movement in the longitudinal direction listening to the same sound with changing pitches (Figure 4b, 5b). In this case, however, the subject was instructed to move his left arm accurately to reach the position where the sound became the same as that at the destination of previous lateral movements, and the subject was also explained that the sound changes only along the longitudinal arm movement but not along the lateral movement. Under these conditions, the subject would understand that the sound is changing as the arm moves longitudinally, but the subject would subconsciously image the lateral movement of the sound owing to the contingent auditory aftereffect. In this design, the subject cannot carry over lateral somatosensory-motor learning nor ignore auditory information during longitudinal reaching movements. If the longitudinal reaching movement is shifted laterally by changes in sound pitches despite subject's intention to move the arm longitudinally, it can be proved that auditory information affected the control of voluntary movements. In practice, we set the following three conditions: the pitch rises (Condition 1) or falls (Condition 2) as the arm moves forward, and the pitch stays at a high level regardless of arm movements (Condition 3). Four patients performed the reaching task in the order of Conditions 2→1→2→1→3→3, and another four did it in order of Conditions 1→2→1→2→3→3.

### 2.1.3. Experimental Setup

All experiments were conducted in a sound-attenuated recording room. Each subject sat down on an exclusive chair with his head fixed. Subject's left hand was initially placed on the table in front and the reaching task was started by extending the hand toward just in front of the body. A polyvinyl fingerstall was put on subject's left fingertip to exclude friction between the finger and the table. The posture at the starting point was also ordered to be a shoulder flexion of 0 degree, shoulder internal rotation of 30 degrees, elbow flexion of 90 degrees, elbow pronation of 90 degrees and wrist flexion of 0 degree (Figure 4).

Reaching to the horizontal plane was detected using the magnetic position sensor, Fastrak (Polhemus Incorporated, USA) attached to the tip of subject's second finger.

The Fastrak sensor can detect 0.08 cm RMS in position and 0.15 degree RMS in angle, with a sampling rate of 60 Hz. A position sensor on the tip of the left second finger sent signals with a frequency of 60 Hz to the computer (Silicon graphics, Japan) that modulated a position change of 25 cm to a spectral change of 0.7 octaves taking 10 msec or less. A pure tone was used as the sound source. The sound volume was set to be 55 dB at the outer ear via a headphone. The sound was given to the subject for a period from 5 seconds before starting reaching to the completion of reaching.

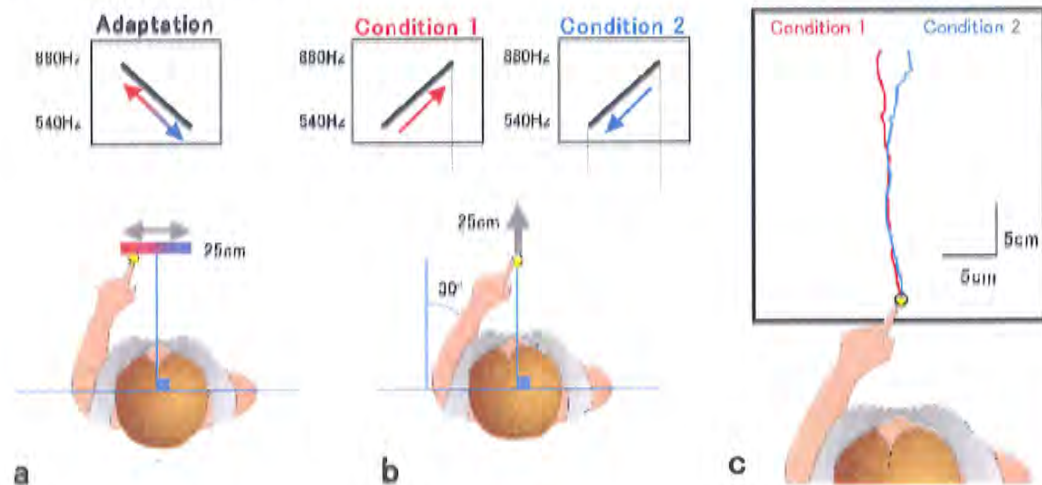


Figure 4. Procedures of the experiment II and typical results. (a) As adaptation (learning), the subject repeatedly moved his left hand in the lateral direction for 10 minutes listening to sounds with changing pitches through headphones. The sound pitch serially increased from left to right by 0.7 octaves in 25 cm (880 Hz at the left side and 540 Hz at the right). (b) Then, the subject was immediately blinded with an eye mask and performed the reaching movement in the longitudinal direction listening to same sound with serially changing pitches. The subject was instructed to move the arm accurately in the longitudinal direction to reproduce the same sound pattern as that in the adaptation trial. The subject was also explained that the sound pitch is changing along the longitudinal direction, not in the lateral direction. Sound pitches were changed from low to high (Condition 1) and from high to low (Condition 2) as the arm moved forward, and the results were compared. (c) Typical results obtained from one subject by two-dimensional analysis: As the arm move forward, the locus of reaching was shifted to the left in Condition 1 and to the right in Condition 2, namely, in the same direction as the adaptation.



## 2.2 Results

As the finger moved forward, the direction of fingertip movement shifted leftward in Condition 1 and shifted rightward in Condition 2 (Figures 5 and 6). The direction of each of these lateral shifts was the same as that could be expected from the contingent auditory aftereffect, except only one subject (Figure 5). The direction of Condition 1 was statistically significantly different from the direction of Condition 2 ( $p < 0.01$ , Welch's modified two sample t-test, Figure 6b). These results prove that voluntary movements are subconsciously affected by auditory feedback in humans.

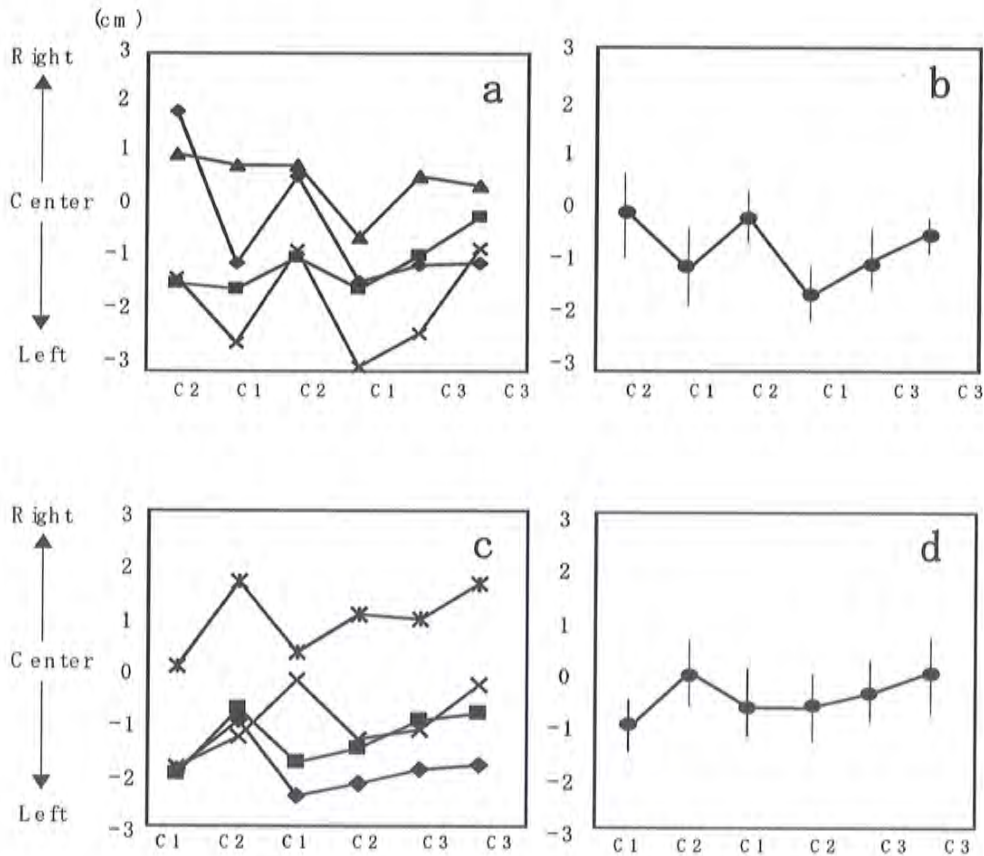


Figure 5. Effects of sound pitch changes on reaching. The X-axis is Conditions, and the Y-axis is the distance of the right and left shifts of the locus. (a) Four subjects performed the task in the order of Conditions 2→1→2→1→3→3, and (c) another four performed it in the order of Conditions 1→2→1→2→3→3. As shown in (a)-(d), the locus of the fingertip consistently shifted leftward in Condition 1 and rightward in Condition 2 as the fingertip moved forward. Differences of shifts between Conditions 1 and 2 were about 1-3 cm that were computed to be 2-7 degrees in terms of a circle with a diameter of 25 cm. Mean values ( $\pm$ S.E.M.) in four subjects in (a) and (c) are shown in (b) and (d), respectively.

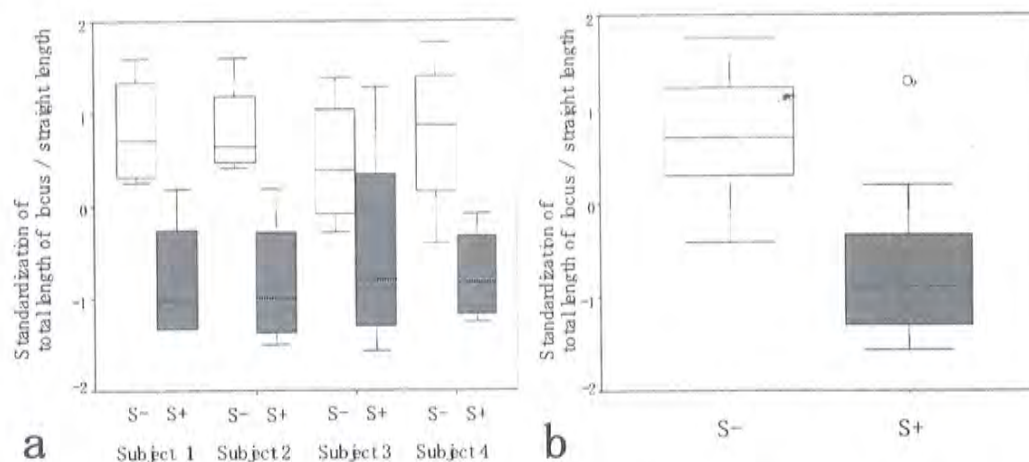


Figure 6. Mean value of lateral shifts on reaching. The X-axis shows Conditions, and the Y-axis is the distance of lateral shifts. (a) Mean value in each subject. (b) Mean value in all eight subjects. The mean value in Condition 1 were statistically significantly different from that in Condition 2 ( $p < 0.01$ , Welch's modified two sample t-test).

### 3. Experiment III: Cortical Networks for Voluntary Hand Action Involving Audiomotor Transformations

In visuomotor integration, goal-directed movements require transformation of visual representations of the environment into muscle-control signals, a process termed visuomotor transformation. The rostral bank of the intraparietal sulcus (IPS), which contains neurons that extract detailed visual information about the nature of the object to be grasped, is connected reciprocally with a ventral premotor area (PMv) within the frontal lobe[7]. This parietofrontal network is involved in monitoring ongoing movements and improving the planning and execution of subsequent hand movements.

Additionally, a specific pathway and neural representation for auditory object information, parallel to the visual system, is suggested by both behavioral [8,9] and neurophysiologic data [10-12]. Linkage between motor planning concerning vocalization and auditory perceptions has been confirmed in humans [13,14]. Calvert et al.[15] reported engagement of the superior temporal sulcus (STS) in integration of auditory information, finding enhanced activity in the STS when subjects both saw and heard a speaker reading a passage, compared to mismatched audiovisual conditions or the audio or visual condition alone.

In studying motor learning of hand movements according to auditory information, some investigators observed activation of the dorsal premotor cortex (PMd) in association with different sensory cues. However, they used a task with externally triggered hand movement, such as simple reaction time determination or a spatial localization task [16-18]. No data were reported concerning the region involved in monitoring ongoing hand movements and improving the planning and execution using auditory information.

In the present study aimed to delineate the cortical network of auditory information for motor control learning of hand movements (audiomotor transformation), and compare it with one subserving visual information.

### 3.1 Subjects and Methods

#### 3.1.1. Subjects

Six right-handed male subjects with no neurologic or psychiatric history participated in this imaging study (age range, 21 to 26 years). All gave informed consent according to procedures approved by the Ethics Committee of the Hiroshima Prefectural Rehabilitation Center.

#### 3.1.2. Experimental Set-up

All experimental tasks were carried out in the MRI room. The MRI scanner had a static magnetic field strength of 1.5 T, a gradient magnetic field strength of 34 mT/m, and a superconductive magnet. Figure 7a illustrates a system of our design for measuring pinch-power signals that was suitable for use near the fMRI scanner (MAGNETOM SYMPHONY, Siemens, Erlangen, Germany).

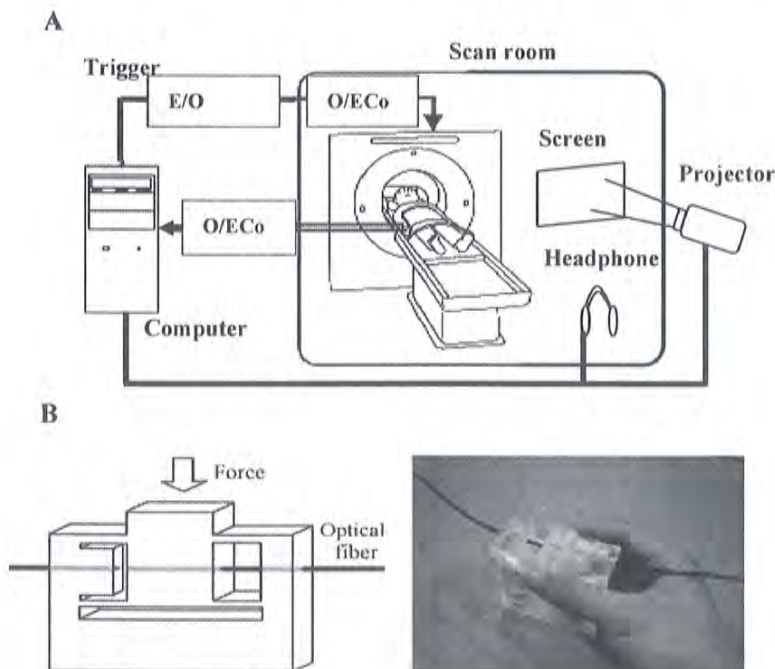


Figure 7. Experimental set-up of the experiment III. The system is accessible in the functional magnetic resonance imaging (fMRI) scanning room, but does not degrade fMRI image data in any way. The subject pinches a pinch-power sensor made of acrylic resin and an optical fiber. The pinch power was visualized with computer graphics to provide visual biofeedback projected on a screen in the scanning room, or auditory feedback with sound-pitch changes heard through a headphone.

The pinch-power signals were measured by a pinch-power sensor that we developed; it was made from an acrylic resin and an optical fiber (Figure 7b). Pinch-power changes could be detected in increments of 0.01 kg. Measured signals were recorded by a personal computer linked to the sensor via an analog/digital converter (sampling frequency, 1.0 kHz; quantization, 12 bits). The computer could send visual or auditory feedback signals within 5 msec after measuring pinch-power signals, so volunteers did not experience a time delay in manipulating the pinch-power sensor using feedback signals. Subjects watched visual feedback signals projected on a screen in the scanning room. The computer modulated a pinch-power change of 2 kg to a position change on the screen. Figure 8 illustrates the visual feedback signals on the screen, where the horizontal dimension displayed time and the vertical dimension displayed pinch power.

Subjects adjusted their pinch force upon the sensor to keep the graphic readout on a target line. They also could use a headphone for auditory feedback. The computer modulated a pinch-power change of 2 kg to a spectral change of pure tone sound according to the relationship,  $f = 523 + \text{pinch force (g)} / 40$  (Hz). Subjects pinched the sensor in a manner that matched the pinch-force tone to the pitch of a target sound (pure tone of 573 Hz).

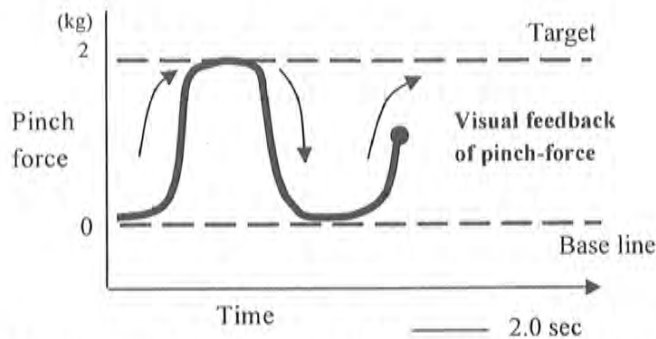


Figure 8. Visual feedback signals on the screen. The horizontal dimension indicated time, and the vertical dimension indicated pinch power. A subject pinched the sensor at a rate of 0.5 Hz, aiming to adjust pinch power according to the target line.

### 3.1.3. Task Procedure

Six paradigms were given serially for each subject to carry out, as outlined below:

*First paradigm (SMP; Somatosensory-motor Pinch):* This required repetitive pinching by the right hand at a rate of 0.5 Hz, with the eyes closed. Subjects adjusted the pinch force to keep the display on the target line (2 kg).

*Second paradigm (VS; Visual Stimulation):* Subjects watched the screen while a waveform similar to VMP (described below) was projected, without pinching the pinch-power sensor.

*Third paradigm (AS; Auditory Stimulation):* Subjects listened through the headphone to spectral changes of pure tone similar to AMP (described below), without pinching the sensor.

*Fourth paradigm (VMP; Visuo-motor Pinch):* Repetitive pinching with the right hand was carried out at a rate of 0.5 Hz, with the eyes open to obtain real-time visual feedback of

pinch power through a mirror providing a view of the screen. Subjects sought adjust the pinch-force readout onto the target line (2 kg).

*Fifth paradigm (AMP; Audio-motor Pinch):* Repetitive pinching with the right hand was carried out at a rate of 0.5 Hz, with eyes closed to obtain real-time auditory feedback of grip power via a headphone. Subjects intended to match the pinch-force tone to the pitch of the target sound (573 Hz, 2 kg).

Each paradigm was organized in an ABAB pattern, in which A involved resting, and B involved performing SMP, VS, AS, VMP, or AMP, with each interval in the pattern lasting through acquisition of 10 volumes. In the resting period of VS and VMA, subjects watched the screen while the baseline and target line were projected. In the resting period of SMP, AS, and AMP, subjects listened through the headphone to spectral changes of pure tone that was modulated to 0 kg. All subjects performed the paradigms in the order from first to fifth. Before VMP and AMP, subjects carried out rehearsal training for 10 min to render the learning effect uniform. The system set-up was exactly the same for all paradigms, and the paradigms did not differ in experimental noise introduced in acquiring imaging data.

#### 3.1.4. Image Data Acquisition

A 1.5-T SYMPHONY system was used to acquire 20 T<sub>2</sub>-weighted transverse echo-planar (EPI) images (FOV, 192 x 192 mm; matrix size, 64 x 64; in-plane resolution, 3 x 3 mm<sup>2</sup>; flip angle, 90; T<sub>E</sub> 60 ms) with blood oxygenation level-dependent (BOLD) contrast. EPIs represented 6.0-mm thick axial slices obtained every 6.0 mm, acquired continuously by an interleaved method during a 3-min session. An automatic shimming procedure was performed before each session. For each subject 51 functional volumes were collected within a single scanning session, with an effective repetition time (T<sub>R</sub>) of 4.4 s/vol. The first volume obtained was discarded to allow for T<sub>1</sub> equilibration effects. Image processing was carried out using SPM2 (Wellcome Department of Imaging Neuroscience, London, UK; see <http://www.fil.ion.ucl.ac.uk/spm>) implemented in MATLAB 6.5 (Mathworks, Sherborn, MA). Images were realigned to the first volume by rigid body transformation, sinc-interpolated over time to correct for phase advance during acquisition, and normalized into standard stereotactic space using the Montreal Neurological Institute template (MNI). Normalized images of 3 x 3 x 6 mm<sup>3</sup> were spatially smoothed by a Gaussian kernel of FWHM 8-8-15 mm [19]. Treating the volumes as a time series, the data were high-pass filtered to 1/120 Hz.

#### 3.1.5. Image Data Analysis

We employed conjunction analyses to test for common activation across the six subjects to determine whether they showed increased activity in a given brain area. We reported activations of voxels corresponding to p values of 0.001 or less, without corresponding by multimodal group analysis. Anatomic identification was carried out by superimposing the maxima of activation foci both on the MNI template and on the normalized structural images for each subject. Areas were labeled using the atlas of Talairach [20].

## 3.2 Results

### 3.2.1. Performance Data

We defined the following quantitative performance index  $J_{Force}$  to evaluate pinch power of each subject during the behavioral task as:

$$J_{Force} = \int F(t)dt$$

where  $F(t)$  indicates a measured signal of pinch power in the experiment. The mean  $J_{Force}$  of six subjects for SP, VNP, and AMP were as follows:

SMP: mean  $J_{Force} = 96.9 \pm 20.8$

VMP: mean  $J_{Force} = 112.7 \pm 8.1$

AMP: mean  $J_{Force} = 103.6 \pm 18.1$

No significant differences were evident between VMG and AMG in the characteristics of pinch power according to a one-sided t test ( $p > 0.05$ ).

**Table 2. Brain regions activated by visuomotor and audiomotor transformation paradigms**

Brain regions (Brodmann's area)	MNI template				Brain regions (Brodmann's area)	MNI template			
	x	y	z	Z-score		x	y	z	Z-score
<b>SMP; somatosensorimotor pinch paradigm</b>									
Right globus pallidus	-16	2	0	4.19					
Left middle frontal gyrus (BA 6)	6	-12	72	4.14					
Right precentral gray matter (BA 6)	-48	-2	54	3.88					
<b>VS; visual stimulation paradigm</b>									
Right middle occipital gyrus (BA 37)	-50	-60	-10	4.26	<b>AS; auditory stimulation paradigm</b>				
Right superior occipital gyrus (BA 17)	-30	-82	24	3.94	Right posterior cingulate (BA 30)	-10	-68	6	4.08
					Right middle temporal gyrus (BA 21)	-68	-14	-4	3.95
					Right paracentral lobe (BA 5)	0	-46	68	3.88
<b>VMP; visuomotor pinch paradigm</b>									
Left inferior frontal gyrus (BA 45)	60	12	18	4.06	<b>AMP; audiomotor pinch paradigm</b>				
Right precuneus (BA 19)	-30	-70	40	3.87	Left suprior temporal gyrus (BA 22)	54	6	0	4.41
Right inferior parietal lobe (BA 40)	-48	-38	32	4.10	Left suprior temporal gyrus (BA 42)	64	-18	12	4.50
Right superior parietal lobule (BA 7)	-16	-74	56	4.36	Right inferior parietal lobule (BA 40)	-62	-36	42	3.95
Left precuneus (BA 7)	16	-72	46	4.44	Left superior frontal gyrus (BA 8)	-4	18	54	4.42

Z-scores correspond to voxels of peak activity whose locations are given as stereotaxic coordinates referring to the atlas of Talairach and Tournoux.

### 3.2.2. Brain Activation

#### 3.2.2.1. Brain Activation in Each Paradigm

We performed group analyses in each paradigm (Table 2). Voxels were identified using a contrast criterion that tested for an average activation over subjects and represented a characterization of group responses using a random effect model ( $p < 0.001$ , uncorrected).

In simple sensory stimulation paradigms such as VS and AS, activations were detected mainly in the sensory association areas: right and left occipital cortices in VS, or right temporal cortex in AS. In the visuomotor transformation paradigms (VMP), activations were

detected mainly in and near the left STS region as well as the PMv and IPS bilaterally. In the audiomotor transformation paradigm (AMP), activations were detected in the left STS.

### 3.2.2.2. Conjunction Analysis Between Visuomotor and Audiomotor Transformation

We performed conjunction analyses for each paradigm (Table 3 and Figure 9). Voxels were identified using a contrast criterion that tested for an average activation over subjects and represented a characterization of group responses according to a conjunction analysis ( $p < 0.05$ , family-wise error, corrected). The conjunction between VS and AS did not show any activation. The left PMv and left STS were significantly activated according to the conjunction between the VMP and AMP. Direct comparisons of cerebral blood flow in the left STS and the PMv showed a signal increase in the VMP and AMP paradigms (Figure 10).

**Table 3. Multimodal cortical regions for visuomotor and audiomotor transformation paradigms**

Brain regions (Brodmann's area)	MNI template			Z-score
	x	y	z	
Right transverse temporal gyrus (BA 42)	66	-22	12	7.68
Left middle frontal gyrus (BA 6)	42	-4	60	6.89
Left middle frontal gyrus (BA 9)	52	2	42	6.43

Z-scores correspond to voxels of peak activity whose locations are given as stereotaxic coordinates referring to the atlas of Talairach and Tournoux.

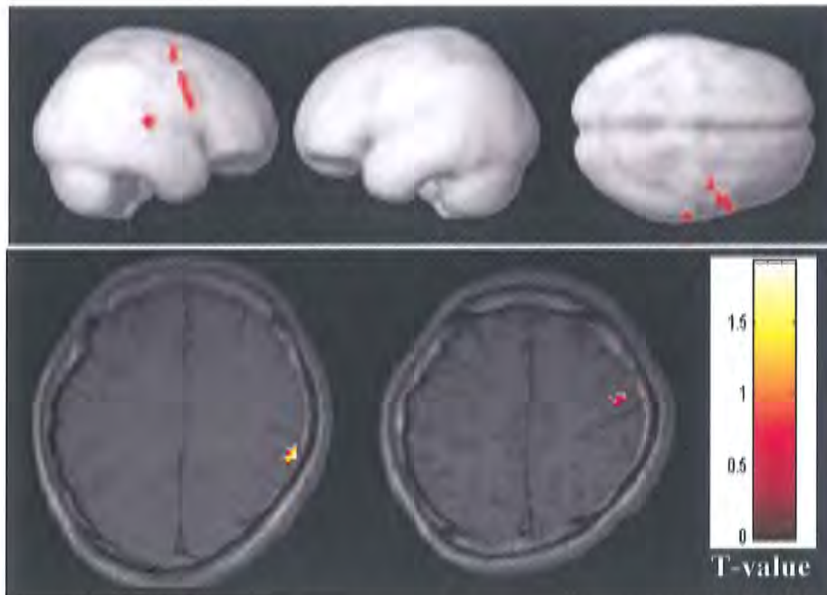


Figure 9. Activation maps resulting from conjunction analysis between VMP and AMP ( $P < 0.05$ ; family-wise error, corrected), showing significant activations of the left PMv and STS. Data correspond to a group analysis of six subjects. Results are displayed on a reference brain (Montreal Neurological Institute; MNI) with Talaraich coordinates indicated. VMP = visuomotor pinch.

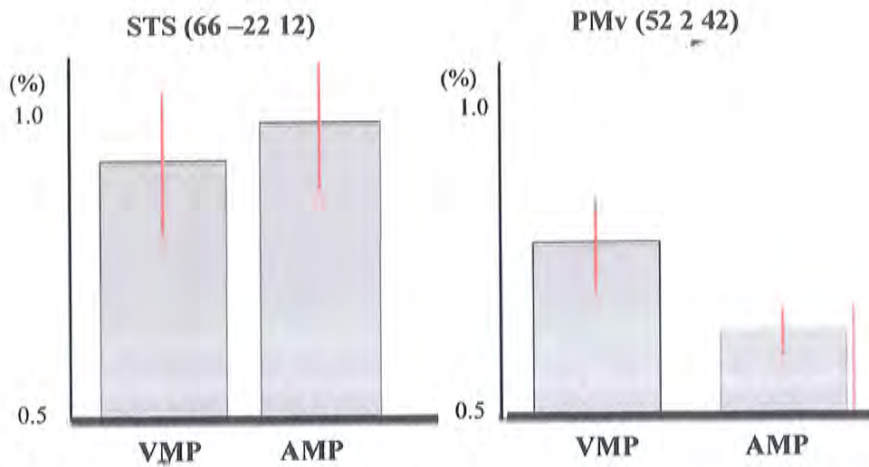


Figure 10. Averaged responses of the left STS and left PMv to the VMP paradigm and AVP paradigm. Similar activations for both paradigms were verified for both areas.

### 3.2.2.3. Modality-Specific Activation in Visuomotor and Audiomotor Transformations

To determine brain regions more active for visuomotor or audiomotor transformation paradigms than for simple motor and simple sensory paradigms, we analyzed the interaction of [VMP – (SMP + VS)] and [AMP – (SMP + AS)]. The term [VMP – (SMP + VS)] showed activity specific for visuomotor transformation as bilateral hemispheric activations in the IPS (Table 4 and Figure 11a). The term [AMP – (SMP + AS)] showed activity specific for audiomotor transformation as left hemispheric activation in the lateral region of the primary auditory cortex (A1) (56 –22 8,  $Z = 5.34$ ; Table 4, Figs. 11b and 12)

**Table 4. Modality specific cortical regions for visuomotor and audio-motor transformation paradigms**

Brain regions (Brodmann's area)	MNI template			Z-score
	x	y	z	
<b>VMP-(SMP+VS)</b>				
Left precuneus (BA 7)	12	-76	56	4.37
Left superior parietal lobe (BA 7)	30	-58	58	4.12
Right precuneus (BA7)	-20	-72	54	3.97
<b>AMP-(SMP+AS)</b>				
Left superior temporal lobe (BA41)	56	-22	8	5.34

Z-scores correspond to voxels of peak activity whose locations are given as stereotaxic coordinates referring to the atlas of Talairach and Tournoux.



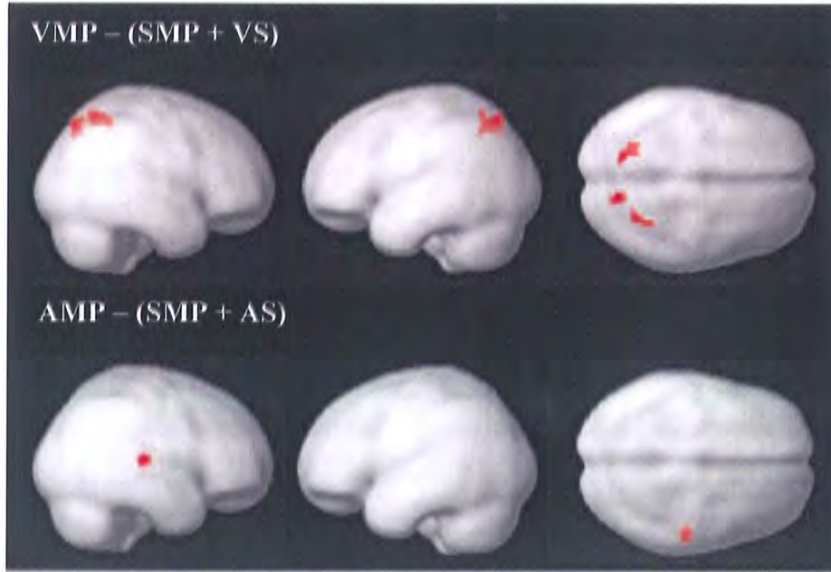


Figure 11. Activation maps showing significant task-related increases in blood oxygenation level-dependent (BOLD) contrast signal ( $P < 0.001$ , uncorrected for multiple comparisons). Data correspond to a group analysis of six subjects. Results are displayed on a reference brain (Montreal Neurological Institute; MNI) with the Talaraich coordinates indicated. (a) Interaction between VMP, SMP, and VS, evaluated as  $[VMP - (SMP + VS)]$  showing activity specific for visuomotor transformation, indicated activation in the left IPS (50 14 34,  $Z = 5.24$ ). (b) Interaction between AMP, SMP, and AS, evaluated as  $[AMP - (SMP + AS)]$ , showing activity specific for audiomotor transformation, indicated activation in the lateral part of the primary auditory cortex (50 14 34,  $Z = 5.24$ ).

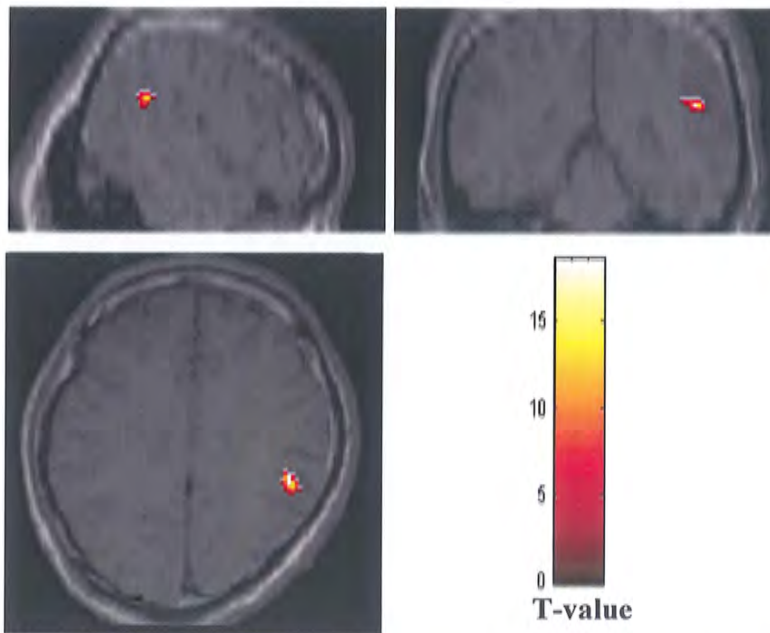


Figure 12. Three-dimensional view demonstrating activation in the lateral part of the primary auditory cortex during audiomotor transformation, evaluated as  $[AMP - (SMP + AS)]$  ( $P < 0.001$ , uncorrected for multiple comparisons).

## 4. Discussion

Our study proves not only that auditory feedback affects controlling of voluntary hand movements in humans, but also that the cortical network on an ongoing pinching task with real-time visual or auditory feedback.

### 4.1. Patients with Deep Sensory Disturbance Can Use Auditory Information to Control Voluntary Movements

In respect of auditory information, a linkage between vocalization and perceptions has been confirmed in humans [21, 22]. However, no data have been reported about the effect of sounds on sensorimotor transformation in the goal directed voluntary movements of limbs. Since humans do not produce any sound linking to limb movements, it appears to be generally believed that humans use auditory information only to perceive outward things.

The effect of sound information in patients with deep sensory disturbance did need little learning because of utilizing natural sounds. It is known that a sound in the vicinity of the face is well localized when it moved laterally in particular [23-25]. In the three subjects (No.2-4) with binaural listening, the variance of finger movement velocities improved in the lateral direction by the use of sound information. On the other hand, the subject (No.1) with monaural listening could demonstrate a marked improvement in the longitudinal direction rather than in the lateral direction. These results suggested that the route passing through sound localization is thought to be the most basic source of information. In patients with deep sensory disturbance, auditory information may have made the frame of reference as the alternative of somatosensory information, and played an important role in controlling voluntary movements. We here propose the presence of audiomotor transformation that belongs to sensorimotor transformation and integrates sound information to control voluntary movements.

The experiment I proves that auditory information affects controlling of voluntary movements in humans. The power of tuning the auditory information in motor control is weaker than that of somatosensory and visual information. If movement-associated sounds can be effectively utilized for learning by introduction of virtual reality techniques for example, the sounds can be utilized as an effective information source for the improvement of voluntary movements in disabled persons.

### 4.2 Auditory Information Affects Voluntary Movements in Healthy Volunteers

When the effect of sound production linking to limb movements on motor control is to be investigated in healthy subjects, there are considerable technical problems because of this unusual situation. It is known generally that when humans pay attention to one sensory modality, other sensory modalities are neglected [26, 27]. In a learning experiment with simultaneous visual and auditory stimuli, the visual cortex is suppressed or unchanged in an

early phase of learning because attention is paid only to the auditory stimulus. However, when the learning has been well established, the visual sense begins to be activated by sound information, and the prefrontal cortex and superior temporal cortex are suggested to participate in this integration [28]. Since healthy subjects can sufficiently control body movements utilizing somatosensory information alone, they can perform an experimental task neglecting puzzling sound information even after the establishment of learning. Thus, we developed the new experimental design utilizing the contingent auditory aftereffect, in which subjects must use auditory information to control voluntary movements conflicting with somatosensory information. The contingent auditory aftereffect used produces an illusion of sound shifting of about 2-4 degrees for every rising or falling change in pitch of 0.7 octaves [6, 29]. Contingent aftereffects have been reported to be present in the visual and auditory sensory systems [29-34]. Therefore, their neural mechanisms are thought to be common to higher associative processing mechanisms [6]. In our study of contingent auditory aftereffect, the frame of reference that had already been learned by utilizing sound [35], may have affected the control of voluntary movements through higher cognitive centers.

The experiment II does not decide whether audiomotor transformation functions as a sound modality-specific integrating unit or utilizes other supramodal integrating units and consequently affects other senses. In macaque monkeys, parallel spatial working memory processes for visuospatial and audiospatial information are present in the dorsolateral prefrontal cortex [34]. Whether healthy subjects possess a modality-specific unit for audiomotor transformation is a matter of the experiment III.

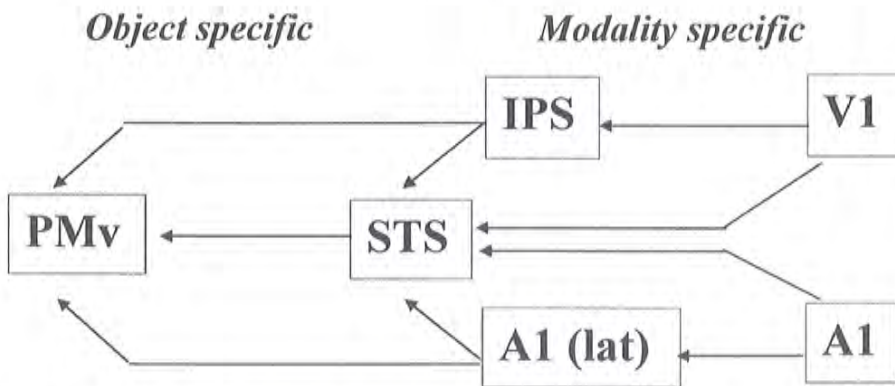


Figure 13. Cortical networks of visual and auditory feedback on hand action. PM; premotor cortex, STS; superior temporal sulcus, IPS; intraparietal sulcus, A1 (lat); lateral region of primary auditory cortex V1; primary visual

#### 4.3. Cortical Networks for Hand Movement Control Involving Auditory Feedback

We investigated both visuomotor and audiomotor transformations using an ongoing pinching task with real-time visual or auditory feedback. Conjunction analysis between the VMP and AMP demonstrated that the same areas of the STS and PMv were involved in both visuomotor and audiomotor performance in controlling the ongoing pinching task. Interaction

analysis between VMP, SMP, and VS showed that right and left IPS were involved in transforming the visual information. Notably, interaction between the AMP, SMP, and AS showed engagement of the left lateral A1 in transforming auditory information. This appears to demonstrate that the left lateral A1 participated in transforming auditory information for executive control of hand movements. In the sensorimotor transformation, visual and auditory information concerning hand movements was transformed to the same STS and PMv via modality-specific cortical networks (Figure 13).

#### *4.3.1. Activation Areas of Premotor Cortex*

Evidence for sensory responses within the monkey premotor cortex in the absence of any movement preparation [35-37] has begun to challenge the presumed functional dichotomy between premotor and parietal areas in favor of a more widely distributed sensorimotor representation including both regions. Many studies of attention to sensory events without motor planning have sought to delineate multimodal sensorimotor networks. Two core hypotheses that were derived from the assumption of activity of the premotor cortex; first, that patterns of attention or execution would be similar regardless of sensory modality ("top-down" modulation), and second, that different sensory modalities engaged different cortical networks in sensorimotor transformation ("bottom-up" modulation). With visual information in the absence of motor planning, the PMv was shown to be engaged in object-specific patterns determined by form [38], size [39, 40], or color patterns [41]. As for auditory information without motor planning, Schubotz et al.[42] demonstrated modality-dependent modulation for auditory events as to which patterns engaged fields for hand movements (PMv), suggesting that premotor areas reflect object properties irrespective of whether the information is provided by vision or audition. Our study supported this view, suggesting that premotor areas reflected execution properties ("top-down" modulation) when feedback information was provided by either vision or audition.

As a counterpart of attention studies, classical serial reaction task studies [43] have demonstrated certain kinds of sensorimotor networks. However, differences in premotor cortex activation areas between visuomotor and audiomotor conditions still provoked controversy. Many reports using a serial reaction task involving different sensory information, however, mentioned activation of the PMd. Bushara et al.[44] reported dissociation of PMd activation in auditory or visual spatial localization tasks. Sugiura et al.[17] compared activated regions in the PMd during simple reaction-time tasks with visual and auditory cues, demonstrating overlap between cue varieties. However, these findings assessed an established association of ballistic movement between sensory input and motor output without ongoing fine movement control using different sensory integrations. Little is known about activation of the PMv for different sensory modalities in the process of monitoring ongoing movements and improving planning and execution (sensorimotor transformation) in humans. We studied PMv involvement in a sensorimotor cortical network with a motor planning paradigm. Our data showed the same area of the left PMv to be involved in both visuomotor and audiomotor transformations, suggesting that the PMv reflected executive dependent properties ("top-down" modulation) whether information was provided by vision or audition.

#### 4.3.2. Activation Areas of Superior Temporal Sulcus

The STS has been suggested to be among the association areas where various kinds of information converge and are processed. In monkeys, Jones and Powell [45] found convergence of somatic, auditory, and visual systems in the depth of the upper two-thirds of the STS. Although the human homologue of the monkey STS still is somewhat controversial [46, 47], several lines of evidence suggest that the human multimodal sensory area is located near the monkey STS: anatomic correspondence between the human and monkey inferior parietal lobe (IPL) [48-50]; functional correspondence between human and monkey IPS [51-54] and the observation that STS lesions in humans and monkeys commonly cause hemispatial neglect, while IPL lesions do not [55-57].

Throughout functional imaging studies [58] and intraoperative studies [59], an area closely corresponding to the monkey STS was suggested to take part in convergence of somatosensory, auditory, and visual information. All of these investigators in primates and nonprimates focused on perception of multimodal sensory information, rather than sensorimotor transformation, therefore not examining audiomotor transformation of hand movements.

With respect to transformation of auditory information, linkage between vocalization and perceptions has been confirmed in humans [13, 14]. Calvert et al.[15] found enhanced activity in the STS when subjects saw and heard a speaker reading a passage compared to mismatched audiovisual and pure audio or visual conditions. This modulation by visual input of activity in the STS also has been shown to occur during lipreading in the complete absence of auditory input [60]. When Calvert et al.[15] presented subjects with visual stimuli of a speaker reading a passage paired with sound from a different point in the passage, they found evidence of suppression near regions of the STS that were enhanced by congruent stimuli.

#### 4.3.3. Activation Areas of Lateral Auditory Cortex

In our study, interaction between AMP, SMP, and AS showed engagement of the left lateral A1 in transforming auditory information. This region has been reported to be involved in transforming auditory information to a higher level of cognition. Petkov et al.[61] reported a functional dichotomy in human auditory cortex that was reflected in different situations of auditory perception. Simple auditory stimulation activated the medial auditory cortex, and also changed in distribution with changes in stimulus frequency and location, showing tonotopic displacement with changes in sound frequency. In contrast, when subjects paid attention in order to make use of auditory information, the lateral region of the left auditory cortex was enhanced in amplitude, showing unaltered changes in sound frequency. Hence, the left auditory cortex attentionally analyzed acoustic features of behaviorally relevant sound. Our data localized this area where sound information was analyzed and transformed to the STS, representing the investigation to demonstrate the effect of auditory information on sensorimotor transformation in ongoing hand movements.

Our study also analyzed interaction between VMP, SMP, and VS. The results confirmed previous data showing that right and left IPS were involved in transforming the visual information. The reaching movement has been studied well to investigate the mechanism of goal directed voluntary movements. Visuomotor transformation is known to monitor and modulate ongoing voluntary movements such as reaching, since the parietal area 5, medial

intraparietal sulcus (MIP) and 7b activate first and continue to be activated even after the activation of dorsal premotor neurons [62, 63].

## Acknowledgements

We would express our sincere thanks to Dr. Koichi Okamoto for his manuscript reviewing, to Mr. Manabu Sato, Mr. Taro Koyama and Mr. Tatsuya Ikeda of C's Lab. Ltd., and Mr. Hideo Kishimoto and Mr. Wang Chun Cheng of Anima Co. Ltd. for their assistance in computer programming, and to Ms. Seiko Sasaki for her assistance in clerk works. This work was supported by the 1998 Proposal-Based RandD Program of The New Energy and Industrial Technology Development Organization.

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